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EXAMINER	
GANGLE, BRIAN J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/030,706	DE LA CUEVA MENDEZ ET AL.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,10,12-16 and 18* is/are pending in the application.

4a) Of the above claim(s) *18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 10, and 12-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and remarks, filed 7/23/2007, are acknowledged. Claims 1 and 4 have been amended. Claims 1-4, 10, 12-16, and 18 are currently pending. Claim 18 is withdrawn as being drawn to a non-elected invention. Claims 1-4, 10, and 12-16 are currently under examination.

Claim Rejections Withdrawn

The rejection of claim 4 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is withdrawn in light of applicant's amendment thereto.

The rejection of claim 1 as being rendered vague and indefinite by the phrase "under appropriate control for selective cell cycle inhibition and/or killing of said target cells," is withdrawn in light of applicant's arguments and amendment thereto.

The rejection of claim 4 as being rendered vague and indefinite by the phrase "carried out on a human or animal body," is withdrawn in light of applicant's amendment thereto.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 10, and 12-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed methods in a target eukaryotic cell *in vitro*, does not reasonably provide enablement for the methods *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant argues:

1. That, with regard to the teachings by Fitzgerald that toxins have unanticipated toxicity in normal tissues, and that the immune response limits the effect, the immune response only limits the duration over which the toxin can be delivered, and that the present invention is

specifically concerned with addressing the toxicity of toxins. Applicant asserts that Fitzgerald does not teach that one would be prevented from obtaining the effect of controlling eukaryotic cell growth with toxins.

2. That Vassaux *et al.* and Fitzgerald *et al.* have no relevance to the instant claims and that it is improper to use these documents as basis for rejecting the instant claims because these authors do not follow the method of the instant application.

3. That the limiting effects of the human immune response cannot apply when the toxin and antitoxin are produced in the cell by expression from a nucleic acid because the toxin and antitoxin would not be exposed to the immune system.

4. That the methods carried out on *Xenopus laevis* embryos (described in the instant specification) and the methods carried out in zebrafish, as described in the Slanchev reference are *in vivo* methods; therefore, the arguments showing that there is no correlation between *in vivo* and *in vitro* results are not applicable. Applicant asserts that, although the constructs are injected at the one-cell stage, they are effective in the developing embryo, thus, the specification does contain evidence of effectiveness *in vivo*. Applicant further argues that the methods carried out on *Xenopus laevis* embryos do not relate to cells in culture, thus a rejection cannot be based on the differences between cells in culture and cells *in vivo*.

5. That "the test to be applied is whether there is a reasonable correlation between the utility disclosed in the application and the claimed activity," and that a rigorous or exact correlation is not required.

6. That it is necessary to take "due account of the nature of the invention, as set out in the Wands factors. Applicant states that the invention relates to a toxin/antitoxin system, the specification shows that the toxin prevents cell proliferation in eukaryotic cells and the antitoxin neutralizes the toxin in eukaryotic cells, and asserts that the examiner has shown no reason to suppose that these effects are dependent on the details of the cell environment or on its cell-cell interactions.

7. That "suitable delivery methods to developed organisms are well known in the art." Applicant asserts that methods are known for the delivery of proteins; for example, localized administration to tissues via injection and targeting via cell-surface proteins. Applicant also

asserts that methods of delivering nucleic acid constructs, containing tissue-specific regulatory sequences, are well known.

8. That the method serves to refine the targeting of the toxin to provided selectivity for the target cells, because the antitoxin protects the non-target cells against low level "leaky" expression of the toxin. Applicant states, "according to the methods of the present invention, the provision of the toxin to target cells is accompanied by provision of the antitoxin to non-target cells." Applicant asserts that Slanchev *et al.* show this by systemic provision of the antitoxin.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, the examiner has not asserted that, based on the teachings of Fitzgerald, one would be unable to practice the claimed method. The examiner referred to Fitzgerald as evidence of the unpredictability of the claimed method. Applicant maintains that the only thing taught by Fitzgerald is that the duration of treatment is limited; however, as those with knowledge of immunology would realize, this is not the only issue raised by Fitzgerald. First, the human immune response is not limited to neutralizing antibodies that develop two weeks after administration of antigen. There are other mechanisms that remove or inhibit foreign molecules. In fact, multiple authors cite the immune response as a hurdle that must be overcome for targeted toxins or drugs. Shadidi *et al.* (Drug Res. Updates, 6:363-371, 2003) and Juliano (Biochem. Soc. Trans., 35:41-43, 2007) discuss the clearance of these agents by the immune system. In addition, the teachings of Fitzgerald are not limited to the duration of treatment. Fitzgerald cites failure of toxins to gain access to cells as a means by which toxin treatments fail, and most importantly, illustrate the unpredictable nature of these types of methods. Applicant states that the unanticipated toxicity of toxins is not an issue, because the instant invention addresses the toxicity and that the presence of the antitoxin would eliminate unanticipated toxicity. However, by definition, this toxicity is unanticipated, and therefore, unpredictable. As an example, the instant invention limits toxicity by the presence of the antitoxin. However, should the targeting of the toxin be less than ideal, it may affect cells that have not been protected by antitoxin. As stated above, Fitzgerald was referenced, not to show that the instant invention is inoperable, but to show that there is unpredictability that is inherent in methods such as these.

Regarding argument 2, Vassaux *et al.* and Fitzgerald *et al.* were not used as the basis for rejecting the instant claims. Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. Vassaux *et al.* and Fitzgerald *et al.* were used as part of one of these considerations (the state of the art). Moreover, contrary to applicant's assertion, Vassaux *et al.* and Fitzgerald *et al.* are relevant to the instant claims. While they do not specifically use the claimed method, they are useful to show what those of skill in the art would have known at the time of invention. Those of skill in the art clearly realize that there is a large body of knowledge that has broad applicability to most subjects within the field of molecular biology, and this knowledge is no less applicable because it does not specifically recite the claimed method.

Regarding argument 3, the examiner agrees that, if the toxin and antitoxin are not exposed to the immune system, the immune response will not limit their effects. However, the claims are not limited to methods where the toxin and antitoxin are not exposed to the immune system. Furthermore, even when the toxin and antitoxin are produced in the cell by expression from a nucleic acid, the nucleic acids must make it into the cell. The claims encompass methods of delivering nucleic acid constructs that would be exposed to the immune system. These constructs would then be susceptible to the limiting effects of the immune response.

Regarding argument 4, according to MPEP 2164.05(a), the state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date, *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004). Therefore, because the reference was published in 2005, the teachings of Slanchev are not relevant to the instant claims. With regard to the "*in vivo*" nature of the experiments in the instant specification, the definition of *in vivo* is "within the living body." Consequently, anything that happens in a cell could technically be considered *in vivo*. However, those of skill in the art would hardly consider experiments performed in a single cell to be *in vivo*. The *Xenopus* experiments only lasted to the mid-blastula stage. This cluster of cells would have been maintained in a cell culture, which makes the method an *in vitro* method. Furthermore, an example showing injection of toxin into a single *Xenopus* cell (even if that cell

grows into a developed organism) does not provide any evidence that the method would work using all methods of administration into any and all developed organisms. Finally, when the toxin/antitoxin are provided into an embryonic cell line and grown into a developed organism, this is the creation of a transgenic animal, which is inherently unpredictable (Sigmund, Arterioscler. Thromb. Vasc. Biol., 20:1425-1429, 2000; Bampton *et al.*, Brain Res., 841:123-134, 1999).

Regarding argument 5, MPEP 2164.02 states that the issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." The examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). In the instant case, one of skill in the art would not consider an example showing that one could inject the toxin and antitoxin into a single cell of a two-cell organism (grown in a cell culture, whether or not it is considered *in vivo*), thus ablating the progeny of that cell, to correlate to methods of treating cancer in fully developed humans, as is encompassed by the claims. Moreover, even when one considers the *Xenopus* experiments as a "working example," this is only one of three examples provided. However, the scope of the required enablement varies inversely with the degree of predictability involved. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also

In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work.

Regarding argument 6, the examiner is fully aware of the considerations to be undertaken when determining whether claims are enabled. In fact, the Wands factors were addressed individually in the previous office action, and will be restated below. The examiner accepts that, within a given cell, the toxin prevents proliferation and the antitoxin neutralizes the toxin. This is not at issue. Applicant argues that the examiner has shown no reason to suppose that these effects are dependent on the details of the cell environment or on its cell-cell interactions. The examiner also agrees with this statement. In fact, as stated in the previous office action, this is what the examiner considers enabled. However, the claims encompass inhibiting cell proliferation in target cells, where those target cells are any given cell or cell type in any given situation. This includes, for example, targeting individual cells within a fully developed organism, or targeting insects within a crop field. Whether the toxin/antitoxin will work once in a cell is not debated, but whether one can reliably deliver the toxin/antitoxin to the target cells is debatable and unpredictable. This targeting and the response of both the microenvironment and the cells themselves is very dependent on "cell-cell interactions" and the "details of the cell environment."

Regarding argument 7, there are methods by which one can deliver both proteins and nucleic acids to cells; however, these methods are unpredictable and have different characteristics depending on what molecule is being delivered in what type of tissue. It is not simply a matter of deciding what cell to target. In the instant case, applicant has only provided one example of what they term "*in vivo*" delivery (injection of toxin into a single *Xenopus* cell in culture). The skilled artisan would clearly realize that one cannot extrapolate the results shown to the full breadth of the claims. Vassaux *et al.* stated that, in 2000 (after the filing date of the instant application), efficient and reliable targeting of cancer cells could not be achieved with current tools (page 22, column 1). In fact, an entire branch of cancer gene therapy research has been devoted to designing controllable and specific genetic toxins. In 2007, Juliano stated that, when using targeted drug delivery, rapid degradation, clearance by mononuclear phagocytes, inability to penetrate into target tissues, and failure to permeate cell membranes are old

challenges that still remain (page 41, paragraph bridging columns 1-2). Juliano further stated that even the most precisely designed moiety is likely to have off-target effects (page 42, column 1, paragraph 3). Shadidi *et al.*, in discussing targeting of cancer cells, stated that the use of natural targeting peptides has been hampered by a short half-life in blood and poor bioavailability in tissues and organs (page 368, column 1, paragraph 1). Shadidi *et al.* further stated that the majority of targeting peptides have been selected by *in vitro* assays or in rodents, but that these peptides do not always behave equally in humans (page 368, column 1, paragraph 2). They also stated that "peptides exhibiting increased serum stability, good bioavailability in tumours will almost certainly be an effective means of targeting therapy regimen *in the future*," (emphasis added) (page 368, column 2). Since they made this statement 4 years after the instant invention, it is clear that these targeting moieties were not available at the time of filing. In summary, while applicant maintains that targeting methods were well known, they have not disclosed examples of any of these. In contrast, there are numerous publications (examples of which are discussed above) that show the unpredictable nature of the various targeting molecules, even up to 7 years after the instant filing date, thus showing that, at the time of the invention, these targeting methods could not have been known or predictable. Moreover, even delivery methods which may seem to be reliable are subject to unpredictability. Applicant suggests that local administration via injection can be used. However, it is not feasible to inject the toxin/antitoxin directly into each target cell and there is no disclosed utility in only administering toxin/antitoxin to only a single cell. If one imagines injection into a tumor, the toxin/antitoxin would merely be delivered to a region. The uptake of each cell could not be reliably predicted. Some cells may or may not take up toxin and/or antitoxin, rendering the control of toxin by antitoxin unpredictable.

Regarding argument 8, applicant is reminded that enablement is determined based on what was known *at the time of invention*. Therefore, what is shown by Slanchev *et al.* is of no consequence. Furthermore, it is understood that the antitoxin protects cells from the action of the toxin. As stated previously, applicant has not shown a predictable method of delivering either toxin/antitoxin genes or the toxin/antitoxin themselves to anything other than individual cells. In addition, applicant states that the effect on the cell is determined by the ratio of toxin to antitoxin. However, the claim requires that the toxin and antitoxin be "under control so as to

obtain selective cell cycle inhibition and/or killing of said target cells." Applicant has shown no means by which the activity of the toxin and antitoxin can be controlled.

As outlined previously, enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims are drawn to methods of inhibiting cell proliferation in target eukaryotic cells by providing within said cells, ParD kid toxin and ParD kis antitoxin, under appropriate control for selective cell cycle inhibition and/or killing of said targets cells.

Breadth of the claims: The claim encompasses all eukaryotic cells, including human cells, and both *in vivo* and *in vitro* use of said method.

Guidance of the specification/The existence of working examples: The specification discloses examples where kid/kis genes are introduced into yeast and human cells *in vitro*, and where said genes were introduced into a single cell of a two-cell stage *Xenopus* embryo. The method using *Xenopus* is regarded by applicant as an *in vivo* method.

State of the art: First, administration of toxins to humans has led to unanticipated

toxicity in normal tissue, and second, the human immune response limits the effects of the toxin (p. 93, col. 1, paragraph 2). While the specification provides examples of the method using cells *in vitro*, there is no evidence to show that the method could be used successfully in humans. Further, the specification does not provide any basis for correlating the *in vitro* results with beneficial effects that could reasonably be expected when said toxins are administered *in vivo* to control cell proliferation in tumor or other cells, although *in vivo* use is clearly encompassed by the claims. The specification is lacking either direct evidence for *in vivo* benefit, or a reasonable basis for correlating the *in vitro* data as exemplified in the instant specification with *in vivo* benefit. Hence, the specification cannot be said to teach how to use the claimed toxins in all eukaryotic cells without undue experimentation. Moreover, while those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are somewhat useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to *in vivo* efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore, it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences In Vitro). Moreover, Dermer (Bio/Technology, 1994, Vol. 12 page 320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant

body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly, it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Further, neither applicant nor the art has shown a predictable method of delivering the kid/kis genes to multiple cells, or to specific cells in a developed organism so that the target cells can be controlled. The only *in vivo* methods shown by applicant have involved manipulation of one or two-celled embryos. This can hardly be considered an *in vivo* method. While these embryos do grow into organisms, it has not been shown how to target cells in the developed organism. Further, it has not been shown that creating a transgenic human by manipulating one or two-celled embryos would lead to predictable results. It is also noted that the claims encompass delivery of kid/kis by the introduction of the kid/kis genes, but also by introduction of the toxin and antitoxin themselves. There is no means provided in either the art or the specification to administer these proteins to target cells *in vivo*; nor is there a means provided for controlling the activity of these proteins.

Therefore, in view of the lack of support in the art and specification for the use of the method with all eukaryotic cells, it would require undue experimentation to use the full scope of the method as claimed; and the entire scope of the claim is not enabled.

New Claim Rejections

35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites the limitation "the human" in line 2. There is insufficient antecedent basis for this limitation in the claim. Parent claim 1 does not refer to a human. Amending the claim to read "a human" would obviate this rejection.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571) 272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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